## REMARKS/ARGUMENTS

Claims 1, 6, 7, 49, 50 and 51 are amended herein. Claims 2-5, 8-9, 12-43, 45-48, 52-54 and 56-107 are canceled without prejudice or disclaimer. Claims 44, 49-51 and 55 are withdrawn. Claims 1, 6, 7, 10-11 and 108 are presently pending.

**Claim Amendments**

Claims 1, 6 and 49 are amended to replace "the anti-CEA MAb" with "the naked anti-CEA MAb" or "said anti-CEA MAb" with "said naked anti-CEA MAb" to conform with antecedent basis support in the preamble to claim 1, which recites "at least one naked anti-carcinoembryonic antigen (anti-CEA) monoclonal antibody (MAb)." The amendment is supported in the published Specification (No. 20040191248) at least at Paragraph [0287].

Claim 1 is amended to replace "naked humanized antibody" with "naked humanized anti-CEA antibody" to conform with the recitation in Claim 1 of a "naked anti-CEA antibody" and to provide uniformity in the claim language. The amendment is supported in the published Specification at least in the Abstract and at paragraph [0080] and [0102].

Claims 6, 7, 49, 50 and 51 are amended to replace "humanized MN-14 antibody" with "naked humanized MN-14 antibody" to conform to the recitation in Claim 1 of a "naked anti-CEA antibody." The amendment is supported in the published Specification at least at paragraph [0108].

Claim 1 is amended to recite that the composition comprising naked anti-CEA MAb in combination with therapeutic agent is more effective for treatment of cancer than either naked anti-CEA MAb or therapeutic agent alone or the sum of the effects of naked anti-CEA MAb and therapeutic agent administered individually. The amendment is supported in the published Specification at least at paragraphs [0003], [0107], [0247], [0249], [0250], [0286], [0287], [0288] and [0294].

Claims 6 and 49 are amended to move the recited amino acid sequences inside the brackets after the recited CDR, for example, "CDR1 (KASQDVGTSVA, SEQ ID NO:20)," to clarify that both the recited sequences and SEQ ID NOs are the sequences of the recited CDR. For example, the amino acid sequence of CDR1 is KASQDVGTSVA, which is identical to SEQ ID NO:20.

**Claim Rejections – 35 U.S.C. § 112**

Claims 1, 6, 7, 10, 11 and 108 were rejected under 35 U.S.C. §112, 1st paragraph for lack of written description support for the term, "100 to 600 mg." The claims are amended to delete that term.

~~Claims 1, 6, 7, 10, 11 and 108 were rejected under 35 U.S.C. §112, 2nd paragraph as~~ indefinite in the use of the term, "concurrent or sequential administration." Applicants note that term has also been deleted from the claims.

Claims 1, 6, 7, 10, 11 and 108 were rejected under 35 U.S.C. §112, 2nd paragraph as indefinite in the use of the term, "the anti-CEA MAb." Claim 1 is amended to recite "the naked anti-CEA MAb," consistent with the preamble which refers to "at least one naked anti-carcinoembryonic antigen (anti-CEA) monoclonal antibody (MAb)."

Claims 1, 6, 7, 10, 11 and 108 were rejected under 35 U.S.C. §112, 2nd paragraph as indefinite in the use of the term, "said naked humanized anti-CEA MAb," which was asserted to lack antecedent basis support. Applicants respectfully submit that antecedent basis is provided in Claim 1(i), which recites that, "the naked anti-CEA MAb...is a naked humanized anti-CEA antibody." Applicants note that the phrase "said naked humanized anti-CEA MAb" has been deleted from Claim 1.

Claims 6 and 7 were rejected under 35 U.S.C. §112, 2nd paragraph as indefinite. The Action asserted that those claims were indefinite because it was unclear what the relationship was between the CDR and the corresponding peptide sequence. The claims are amended to move the corresponding peptide sequences into parentheses, following the listed CDRs and joining the SEQ ID NOs. Applicants respectfully submit that the skilled artisan, reading for example "CDR1 (KASQDVGTSVA, SEQ ID NO:20) would understand that the listed peptide sequence is the amino acid sequence of CDR1, and is identical to SEQ ID NO:20.

**Claim Rejections – 35 U.S.C. § 103**

Claims 1 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Primus et al. (U.S. Patent 4,818,709) (hereafter "Primus") in view of Queen et al. (5,530,101) (hereafter "Queen").

Claims 1, 6, 7, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al. (Cancer 71:3478-85, 1993; hereafter "Hansen I") or Hansen et al. (U.S. 5,874,540; hereafter "Hansen II) in view of Queen.

Applicants initially note that Claim 108 is not rejected over any of the prior art. Since the 112 rejections are overcome by the instant amendments, Applicants submit that at least Claim 108 is allowable and request a decision to that effect.

The remaining prior art rejections are addressed together, as Applicants submit that amended Claim 1 and dependent Claims 6, 7, 10 and 11 contain an element that is missing from all of the cited prior art, either alone or in combination, including the references of Primus, Queen, Hansen I and Hansen II.

Specifically, amended Claim 1 now recites a composition comprising at least one naked, humanized [Class III] anti-CEA MAb and at least one therapeutic agent, wherein "the combination of naked anti-CEA MAb and therapeutic agent is more effective for treatment of cancer than either naked anti-CEA MAb or therapeutic agent alone or the sum of the effects of naked anti-CEA MAb and therapeutic agent administered individually." I.e., the combined composition has a synergistic anti-cancer effect that is more effective than either agent alone or than the sum of the effects of the individual components.

The unexpected and surprising nature of this synergistic characteristic of the claimed composition is emphasized at numerous places in the published Specification. For example, Paragraph [0107] recites that, "A naked Class III anti-CEA antibody as described herein can significantly increase the chemosensitivity of cancer cells to one or more therapeutic agents. Example 2 discusses the effect of combination therapy of naked hMN-14 and DTIC on human medullary thyroid tumor cells. Paragraph [0247] states that, "Surprisingly, the effects of MN-14 alone and DTIC alone were not additive. In other words, given the results of treatment with 250 μg hMN-14 alone and 100 μg DTIC alone, one would not predict that the combination of 250 μg hMN-14 and 100 μg DTIC would have such a pronounced effect. See FIG. 1A." FIG. 1A shows that addition of naked MN-14 to 100 μg DTIC produced a large increase in efficacy, that was more than the sum of the effects of MN-14 and DTIC individually. Paragraph [0249] states that, "The 75 µg dose of DTIC in combination with this schedule of hMN-14 antibody was significantly more effective than either treatment alone ($p<0.02$). Unexpectedly, the results of combined DTIC and MAb therapy were not additive. At 7 weeks, 8/10 mice in the 75 µg DTIC and MAb group had no palpable tumor, compared to 1/10 mice in the 75 µg DTIC only group and 0/10 mice in the untreated and MAb group." Paragraph [0250] discloses that, "Combined therapy of the naked anti-CEA antibody with DTIC augments the anti-tumor effects of antibody or chemotherapy alone, without increased toxicity. The superiority of the combined modality treatment was surprising." Paragraph [0286] discusses the combination of naked anti-CEA antibody with DTIC for therapy of medullary thyroid cancer (MTC) in nude mice and concludes that, "The 75 µg dose of DTIC in combination with this schedule of hMN-14 was significantly more effective than either treatment alone ($P<0.02$)."

Example 7 discusses the effects of combined naked anti-CEA plus DITC therapy of MTC. Paragraph [0287] summarizes that, "This is the first evidence of tumor suppression with a "naked" anti-CEA MAb. However, combined therapy of the naked anti-CEA MAb with DTIC augments the anti-tumor effects of antibody or chemotherapy alone, without increased toxicity."

Example 8 summarizes the results of another MTC treatment study and Paragraph [0288] reports that, "Naked hMN-14 CEA Mab treatment showed a significant effect on inhibiting tumor growth. When combined with DTIC, a surprisingly enhanced level of inhibition of tumor growth occurred relative to either treatment alone."

Example 9 describes the effects of anti-CEA MAb and CPT-11 on metastatic lung cancer. Paragraph [0294] states that, "The results show that co-administration of hMN-14 and CPT-11 to nude mice bearing GW-39 lung micrometastases increases survival beyond the effect of either modality alone."

Thus, there is ample evidence in the instant disclosure for a surprising and unexpected synergistic effect on cancer of the combination of naked humanized anti-CEA MAb and therapeutic agent. This element of claim 1 is found nowhere in any of the cited prior art, either alone or in combination.

Primus merely discloses methods of immunoassay, using different forms of anti-CEA antibodies, and has very little to say about therapeutic use of such antibodies for the treatment of cancer. Primus provides no teaching or suggestion to combine naked humanized anti-CEA

MAbs with one or more therapeutic agents and clearly provides no reasonable expectation of success in achieving a synergistic effect of such a combination.

Hansen I discloses a panel of anti-CEA monoclonal antibodies, including MN-14, but provides no teaching or suggestion with respect to humanized anti-CEA MAbs, or to make and use the claimed combination of naked humanized anti-CEA MAbs with one or more therapeutic agents. Hansen I also provides no reasonable expectation of success in achieving a synergistic effect of such a combination.

Hansen II discloses humanized anti-CEA MAbs and provides the CDR sequences of instant claim 6, but again provides no teaching or suggestion to make and use the claimed combination of naked humanized anti-CEA MAbs with one or more therapeutic agents. If anything, Hansen II leads the skilled artisan away from the claimed combination, by leading the artisan to the use of immunoconjugates, comprising humanized anti-CEA MAbs directly conjugated to one or more therapeutic agents. Applicants submit that the use of antibodies directly conjugated to therapeutic agents is significantly different and patentably distinct from the instant claimed methods, wherein the therapeutic agents are (by definition) not conjugated to the naked humanized anti-CEA MAbs (otherwise, they would not be "naked"). The teachings of Hansen II with respect to immunoconjugates comprising antibodies directly conjugated to therapeutic agents may be found in numerous places in Hansen II, for example at Col. 2, lines 22-28:

> Still another object of the invention is to provide compositions comprising the antibodies for use in diagnosis and therapy. In this regard it is an object of the invention to provide conjugates comprising the antibodies complexed with imaging agents and therapeutic agents for ex vivo and in vivo imaging, diagnosis, prognosis and therapy, among others.

At Col. 10, lines 14-20 Hansen II states that,

> For therapy with cytotoxic agents, the antibodies are conjugated to any of a variety of known therapeutic agents such as doxorubicin, methotrexate, taxol, ricin A, radioactive atoms, cytoxic agents, and the like, formulating such conjugate in a pharmaceutically acceptable sterile vehicle, and administering the formulation by conventional means.

Nowhere does Hansen II teach or suggest the instant claimed combination of a naked humanized anti-CEA MAb with therapeutic agent, nor does Hansen II provide any hint that the claimed combination may exhibit synergistic anticancer effects, wherein "the combination of naked anti-CEA MAb and therapeutic agent is more effective for treatment of cancer than either naked anti-CEA MAb or therapeutic agent alone or the sum of the effects of naked anti-CEA MAb and therapeutic agent administered individually," as recited in instant Claim 1.

Queen does not even discuss naked humanized anti-CEA MAbs or their use, focusing instead on humanized antibodies against the human IL-2 receptor. There is no teaching or suggestion in Queen to combine naked humanized anti-CEA MAbs with therapeutic agents and no suggestion that such a combination may provide synergistic effects on cancer, as recited in instant claim 1.

None of the cited references contain the slightest hint that the combination of a naked humanized anti-CEA antibody and therapeutic agent may synergistically affect cancer, wherein "the combination of naked anti-CEA MAb and therapeutic agent is more effective for treatment of cancer than either naked anti-CEA MAb or therapeutic agent alone or the sum of the effects of naked anti-CEA MAb and therapeutic agent administered individually" as recited in Claim 1. As this element is missing from all of the cited prior art, alone or in combination, a prima facie case of obviousness has not been established. Further, without any teaching, suggestion or even a mere hint that such a combination might exhibit such an effect, the skilled artisan could have had no reasonable expectation of success in achieving the claimed invention. The lack of reasonable expectation of success also precludes the establishment of a prima facie case of obviousness.

Applicants respectfully submit that in the absence of a prima facie case of obviousness, rejection of the amended claims under 35 U.S.C. §103 is improper. Reconsideration and withdrawal of the rejection are requested.

## Conclusion

For the reasons stated above, Applicants submit that the amended claims are in condition for allowance and request withdrawal of the rejections.

Respectfully submitted,

Dated: April 2, 2007

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